CHEMICAL MANUFACTURERS ASSOCIATION

May 14, 1998

Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens, MD WC-05
P.O. Box 12233
Research Triangle Park, NC 27709

RE: Response to the Call for Public Comments on the recommendation to list "Strong Inorganic Acid Mists Containing Sulfuric Acid" for Inclusion in the Report of Carcinogens, Ninth Edition.
63 Fed. Reg. 13418-20 (March 19, 1998)

Dear Dr. Jameson:

On behalf of the Chemical Manufacturers Association's (CMA) Inorganic Acid Mists Panel and in response to the Call for Public Comments issued in the Federal Register Notice of March 19, 1998, I am providing comments and information regarding "Strong Inorganic Acid Mist Containing Sulfuric Acid," which has been recommended for listing in the *Report on Carcinogens, Ninth Edition.*[1]

It is the opinion of the Panel that the actions of the RG1, the RG2 and the NTP Board Subcommittee regarding "Strong Inorganic Acid Mists Containing Sulfuric Acid" were based on the International Agency for Research on Cancer 's (IARC) previous classification of Occupational Exposure to Strong Inorganic Acid Mists Containing Sulfuric Acid" as a known human carcinogen. Also, it is the Panel's opinion that the original classification by IARC was not justified by

[1] The Inorganic Acid Mists Panel includes the following organizations: Kennecott Utah Copper, ASARCO, Inc., BHP Copper, Phelps Dodge, General Chemical Corporation, DuPont Chemicals, Rhone-Poulenc, Inc., Cypress Amax, Noranda, Inc., PVS Chemicals, Inc., AlliedSignal, Inc., and the National Mining Association

the scientific evidence available at the time of their monograph meeting. Since then, new evidence has been published that provides additional support to the Panel's opinion that many of the key studies relied on by IARC are flawed. Further, based on the outcome of the most recent IARC monograph meeting, we believe that IARC is now requiring a more appropriate level of evidence before classifying substances as carcinogens and it would be appropriate for the NTP to follow this lead.

We urge the NTP to give serious reconsideration to our comments. Our comments focus on:

- the results of the recent IARC monograph meeting;
- a critique of five studies identified in the NTP "Draft Background Document for Strong Inorganic Acid Mist Containing Sulfuric Acid" dated September 26, 1997;
- a critique of the section on the possible mechanism of carcinogenesis in the same document ; and
- a discussion of negative animal studies.

The scientific information available on "Strong Inorganic Acid Mist Containing Sulfuric Acid" is inadequate to conclude that "Strong Inorganic Acid Mist Containing Sulfuric Acid" is either a known human carcinogen or that it can be reasonably anticipated to be a human carcinogen. We hope that after careful review of the data, the NTP will reach the same conclusion.

IARC February 1998 Monograph Meeting

At the February 1998 meeting, the IARC Working Group took a very critical approach to the evaluation of epidemiology studies, resulting in scientifically defensible classifications. If this same working group were to look at all the scientific data on "Strong Inorganic Acid Mist Containing Sulfuric Acid" available today, the Panel believes that IARC would conclude that the epidemiological evidence is inadequate.

During this February 1998 IARC meeting, acrylonitrile, methylene chloride, and chloroprene were considered for change in their classifications based on epidemiological evidence. All of these chemicals had multiple epidemiological studies available for review. The results of these studies were variable. Some studies showed positive associations with cancer and others showed no associations. For both methylene chloride and chloroprene, the epidemiological evidence was concluded to be inadequate. For acrylonitrile,

newer studies were negative, so the Working Group concluded that the classification for this chemical should be downgraded from "limited" to inadequate. The Panel believes that the epidemiologic data base for "Strong Inorganic Acid Mist Containing Sulfuric Acid" is similar to that for acrylonitrile in that there are newer studies that were not considered by IARC. In fact, the most recent study by Coggan *et al.* with the highest reported worker exposures had less than expected rates for both cancer of the larynx and lung.[2] In addition, a reanalysis of the Soskolne *et al.* study, which had the highest reported excess of cancer of the larynx, actually shows a decline in incidence of cancer of the larynx when a more conventional measure of exposure (cumulative dose) is used.[3] The entire epidemiologic data base for "Strong Inorganic Acid Mist Containing Sulfuric Acid" can best be described as inconsistent and conflicting relative to cancers of the larynx or lung. Given this situation, the Panel believes that IARC should conclude the epidemiologic data is inadequate.

A careful review of these comments and our previously submitted August 1997 comments (attached) should allow the NTP to conclude that the evidence for "Strong Inorganic Acid Mist Containing Sulfuric Acid" is inadequate because of the potential for confounding in most studies, lack of exposure verification in many studies, and because of major conflicts and inconsistencies between studies.

Review of Primary Studies Identified by the NTP

Two of the primary studies relied on by the NTP were population studies where exposure to acid mists was presumed based upon occupational titles.[3,4] It is generally accepted that these types of studies are inadequate to classify a compound as a carcinogen. In addition, other similar studies noted in our previous comments showed a negative association. The nested case-control study by Soskolne *et al.* reported the strongest positive association between acid mist exposure and cancer of the larynx; however, a subsequent reanalysis of this

[2] Coggon, D., Pannett, B., Wiel, G. Upper Aerodigestive Cancer in Battery Manufacturers and Steel Workers Exposed to Mineral Acid Mists. *Occupational and Environmental Medicine*, 1996; 53:445-49.

[3] Soskolne, C. L., Jhangri, G.S., Siemiatycki, J., et al. Occupational Exposure to Sulfuric Acid in Southern Ontario, Canada, in Association with Laryngeal Cancer. *Scand J Work Environ Health*, 1992; 18:225-232.

[4] Siemiatycki, J. Ed. *Risk Factors for Cancer in the Workplace*, Boca Raton, FL, CRC Press, 1991

study using a more appropriate measure of worker exposure produced a negative association.[5,6] The two remaining studies used the same cohort of workers. One by Steenland and Beaumont reported an increase in lung cancer.[7] This result was not statistically significant and is the opposite of a more recent study with higher reported worker exposures.[2] The other by Steenland *et al.* is an update of an earlier study published in 1988.[8,9] Both of these studies show approximately a two-fold increase in cancer of the larynx; however, there is no indication of a positive dose-response in either study. Also, these results are in contrast to a negative study where worker exposures were greater.[1]

Of the five primary studies reviewed by the NTP, two had no confirmation of exposure, one is not statistically significant, one is refuted by a subsequent reanalysis of the same data, and the other lacks a finding of a positive dose response. All five studies are in conflict with other studies that used similar methodology. Based on the most recent IARC Monograph Meeting, it is the opinion of the Panel that the epidemiological evidence is inadequate to list "Strong Inorganic Acid Mist Containing Sulfuric Acid" as a known human carcinogen or as reasonably anticipated to be a human carcinogen.

Possible Mechanism of Carcinogenesis

The discussion on page RC-1 of the NTP's draft background document which states that low pH is the most likely mechanism to cause cancer is not supported by the facts. There is very limited evidence one way or the other regarding possible mechanisms. In fact, the NTP Board subcommittee was very critical of the conclusions stated in this section. They indicated that the conclusions were too strong and were not supported by the available evidence.

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[5] Soskolne, C. L., Zeighami, E.A., Hanis, N. M., et al. Laryngeal Cancer and Occupational exposure to Sulfuric Acid. *American Journal of Epidemiology*, 1984; 120:358-369.

[6] Suarez-Almazor, M.E., Soskolne, C., Fung, K., Jhangri, G.S. Empirical Assessment of the Effect of Different Summary Worklife Exposure Measures on the Estimation of Risk in Case-Referent Studies of Occupational Cancer. *Scand J Work Environ Health*, 1992; 18:233-241.

[7] . Steenland K., Beaumont, J. Further Follow-up and Adjustment for Smoking in a Study of Lung Cancer and Acid Mists. *Am J Ind Med.*, 1989, 16: 347-354.

[8] Steenland, K., Schnorr, T., Beaumont, J., Halperin, W., et al. Incidence of Laryngeal Cancer and Exposure to Acid Mists. *British Journal of Industrial Medicine*, 1988, 45:766-776.

[9] Steenland, K. Laryngeal cancer Incidence Among Workers Exposed to Acid Mists (United States). *Cancer Causes Control*. 1997, 8: 34-38.

Animal Carcinogenicity Studies

Swenberg reviewed an EPA sponsored life time study using hamsters exposed to very high doses of sulfuric acid mist.[10] In that study there was no evidence of carcinogenicity, co-carcinogenicity or cancer promotion. There were also two life time animal studies in rats and guinea pigs sponsored by the NIEHS in the mid-1970s. Both of these studies were negative. While they were not formally published, the results are certainly available to the NTP for evaluation. It is very unusual for a substance to be negative in animal carcinogenicity studies with very high exposures in multiple species and be a human carcinogen. The results of these animal studies should prompt a very thorough review of the epidemiological evidence. Once that review is complete, the Panel is confident that NTP will conclude that the epidemiologic evidence is conflicting, inconsistent, and, therefore, inadequate to classify "Strong Inorganic Acid Mist Containing Sulfuric Acid" as to carcinogenicity.

The Panel appreciates the opportunity to submit these comments. You may direct any questions to Ms. Chris B. Trent at (703) 741-5627.

Sincerely yours,

Courtney Price

Courtney M. Price

Attachment

[10] Swenberg, J.A., Beauchamp, Jr., R.O., A review of the Chronic Toxicity, Carcinogenicity, and Possible Mechanism of Action of Inorganic Acid Mists in Animals, *Critical Reviews in Toxicology*, 1997, 27:253-259.

CHEMICAL MANUFACTURERS ASSOCIATION

August 22, 1997

Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens, MD WC-05
P.O. Box 12233
Research Triangle Park, NC 27709

RE: Response to the Nomination of Sulfuric Acid Mist for Inclusion in the Report of Carcinogens, Ninth Edition. 62 Fed. Reg. 37272 (July 11, 1997)

Dear Dr. Jameson:

This letter is submitted on behalf of the Chemical Manufacturers Association-Inorganic Acid Mists (CMA-IAM) Panel in response to the Call for Public Comments issued in the Federal Register Notice of July 11, 1997.[1] Specifically, we are providing comments and information regarding Sulfuric Acid Mist which has been nominated for consideration of listing in the Report on Carcinogens, Ninth Edition.

It is our opinion, supported by the scientific experts that we have consulted, that the scientific information available on Sulfuric Acid Mist is inadequate to conclude that Sulfuric Acid Mist is either a known human carcinogen or that it can be reasonably anticipated to be a human carcinogen.

We suspect that the nomination of Sulfuric Acid Mist is based on the listing by the International Agency for Research on Cancer (IARC) of "occupational exposure to strong inorganic acid mist containing sulfuric acid" as a known human carcinogen and/or the listing of the American Conference of Governmental Industrial Hygienists (ACGIH) of "sulfuric acid contained in strong inorganic acid mists" as a suspect human carcinogen.

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1 The Inorganic Acid Mists Panel includes the following organizations: Kennecott Utah Copper, ASARCO, Inc., BHP Copper, Phelps Dodge, General Chemical Corporation, DuPont Chemicals, Rhone-Poulenc, Inc., Cypress Amax, Noranda, Inc., PVS Chemicals, Inc., AlliedSignal, Inc., and the National Mining Association.

The attached comments will present information demonstrating that sulfuric acid mist is not a carcinogen in animals even in lifetime studies with exposures to extremely high levels of sulfuric acid mist. We will also provide references to additional epidemiological studies that were not available at the time of the IARC review. One of these studies casts doubt on the conclusions of a key study considered by IARC, and another study, with higher workplace exposures than many previous studies, was negative for any excess of respiratory tract cancer. We believe this more recent information demonstrates that the overall scientific information is inadequate to classify sulfuric acid mist as a known or potential carcinogen.

A more detailed review of the CMA-IAM Panel's position follows. The Panel appreciates the opportunity to submit these comments. Please direct any questions you may have to Ms. Chris B. Trent, Manager of the Inorganic Acid Mists Panel, at (703) 741-5627.

Sincerely,

Courtney Price

Courtney M. Price
Vice President, CHEMSTAR

Enclosures

SUBMITTED TO THE
NATIONAL TOXICOLOGY PROGRAM

COMMENTS OF THE CHEMICAL MANUFACTURERS ASSOCIATION INORGANIC ACID MISTS PANEL

ON THE INTENDED LISTING OF SULFURIC ACID MIST IN THE REPORT ON CARCINOGENS, NINTH EDITION

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August 22, 1997

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EXECUTIVE SUMMARY

The Chemical Manufacturers Association Inorganic Acid Mists Panel hereby submits comments on the proposed action by the National Toxicology Program to list Sulfuric Acid Mists in the Report on Carcinogens, Ninth Edition. The Panel makes the following points:

- The CMA-IAM Panel believes that the IARC (International Agency for Research on Cancer) classification of "occupational exposure to strong inorganic acid mist containing sulfuric acid" as a known human carcinogen was inappropriate considering the data available to IARC at the time of that monograph meeting. As with any decision which involves judgment (scientific or otherwise) there may be differing opinions among experts. A review by epidemiologists from the University of Alabama, Birmingham (UAB), which considered the same data as IARC, concluded the evidence for a relationship between cancer of the larynx and "occupational exposure to strong inorganic acid mist containing sulfuric acid" was limited.[1]

- The American Conference of Governmental Industrial Hygienists (ACGIH), which based their classification in part on the IARC classification, indicated in an explanation of their decision that the "available epidemiologic studies are conflicting or insufficient to confirm an increased risk of cancer in exposed humans." Both the UAB and ACGIH reviews suggest that the data considered by IARC more appropriately supported a conclusion that "occupational exposure to strong inorganic acid mist containing sulfuric acid" was a possible rather than a known human carcinogen.

- Additional information which was not considered by IARC, UAB, or the ACGIH is now available. This includes lifetime animal studies which were negative and additional epidemiologic studies that do not replicate previously reported results.

The CMA-IAM Panel asserts that the available scientific evidence is inadequate to support classification of sulfuric acid mists as a known carcinogen or as reasonably anticipated to be a human carcinogen. Studies have been conducted in three animal species involving lifetime exposures to high or very high levels of sulfuric acid mist. No respiratory tumors due to exposure to sulfuric acid mist resulted during these studies. In addition, flaws have been identified in all of the epidemiology studies which have shown a positive association between exposure to sulfuric acid mist and cancer of the larynx. There are also significant inconsistencies among similarly designed studies. The scientific evidence must be looked at in its entirety before a carcinogen classification can be assigned.

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INTRODUCTION

The Chemical Manufacturers Association Inorganic Acid Mist (CMA-IAM) Panel is pleased to submit these comments to the National Toxicology Program in response to its notice of intent to list sulfuric acid mist in the Report on Carcinogens, Ninth Edition. 62 Fed. Reg. 37272 (July 1, 1997). Members of the CMA-IAM Panel include producers and users of sulfuric acid in the U.S. and Canada.[1]

The Panel supports the efforts of the NTP in identifying those materials which may be hazardous to human health; however, we urge the NTP to consider the Panel's comments and review all of the available scientific evidence before proceeding with such action with sulfuric acid mist.

Section I of the comments addresses the IARC decision to classify occupational exposure to strong inorganic acid mist containing sulfuric acid as a known human carcinogen.

Section II of these comments discusses the decision of the ACGIH to classify sulfuric acid contained in strong inorganic acid mists as a suspected human carcinogen.

Section III of these comments reviews animal studies while Section IV reviews epidemiology studies.

I. IARC CLASSIFICATION

At the October 1991 IARC monograph meetings , an epidemiology work group reviewed sulfuric acid and recommended that it be classified as a known human carcinogen. When this recommendation was presented to the full IARC panel, it provoked much argument and debate that resulted in a "compromise" position. IARC elected to not classify "sulfuric acid" at all, and instead established a classification for an "occupational exposure".

The final classification was "occupational exposure to strong inorganic acid mist containing sulfuric acid" as a known human carcinogen. This classification

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1 The Inorganic Acid Mists Panel includes the following organizations: Kennecott Utah Copper, ASARCO, Inc., BHP Copper, Phelps Dodge, General Chemical Corporation, DuPont Chemicals, Rhone-Poulenc, Inc., Cypress Amax, Noranda, Inc., PVS Chemicals, Inc., AlliedSignal, Inc., and the National Mining Association.

leaves open the possibility that other workplace exposures that coexisted with sulfuric acid may have been the real etiologic agents.

This situation is similar to the IARC classification of "isopropyl alcohol manufacture (strong-acid process)" as a known human carcinogen. Isopropyl alcohol is not considered to be a carcinogen, but rather some other factor in the manufacturing process is thought to have been responsible for the epidemiological findings. In fact, exposure to alkyl sulfates, which are a confounding exposure in many studies of sulfuric acid, has been suggested as a more likely etiologic agent than isopropyl alcohol. It is important that the NTP be cognizant of the distinctions between IARC's classification of a manufacturing process compared to IARC's classification of specific chemical substances.

IARC has classified both specific agents (including chemical substances) and manufacturing processes as to their carcinogenic potential. Manufacturing processes have been classified when there is doubt regarding the specific etiologic agent(s) in the workplace. When a manufacturing process is chosen for classification it implies significant doubt regarding the true etiologic agent. A major criticism of the epidemiologic studies regarding acid mist and cancer of the larynx is the lack of exposure measurements. In fact, many of the studies relied on information regarding a person's occupation and industry and tried to make educated assumptions about whether or not they might have been exposed to acid mist. In addition, virtually all of the workplaces studied had potential exposures to other known or suspected respiratory tract carcinogens.

We believe both of these factors were important in IARC's decision to use a manufacturing process classification as opposed to a chemical specific classification. As with the example of isopropyl alcohol manufacture, the chemical named with the manufacturing process may not be the etiologic agent for the observed excess of cancer. We believe this same situation applies to the classification of "occupational exposure to strong inorganic acid mist containing sulfuric acid" as a known human carcinogen. In this case, we believe the evidence does not support classifying sulfuric acid mist per se.

The CMA-IAM Panel believes the IARC classification of "occupational exposure to strong inorganic acid mist containing sulfuric acid" as a known human carcinogen was incorrect. A paper by Sathiakumar, et al. reviewed the same data as the IARC panel and concluded that "the current epidemiologic data alone do not warrant classifying mists containing sulfuric acid (MSA) as a definite human carcinogen."[1] They further stated that "given the multiple exposures in the work environment of which MSA is a part, it is possible that some correlate of exposure to MSA, rather than MSA, causes larynx cancer."

We understand that the NTP has made a decision not to classify manufacturing processes since they were not included in the legislation requiring the development of the Reports on Carcinogens. We believe it is therefore inappropriate for NTP to use the IARC classification of a manufacturing process as a basis to classify sulfuric acid mist per se.

II. ACGIH CLASSIFICATION

The ACGIH has classified "sulfuric acid contained in strong inorganic acid mists" as a suspect human carcinogen. This classification was done as part of a general update on carcinogen classifications and was based mainly on the earlier IARC classification. The CMA-IAM Panel had asked for an opportunity to provide comments directly to the Dust and Inorganics Subcommittee and had been assured of an opportunity to do so. We had also provided copies of additional studies to the ACGIH for distribution to the Dust and Inorganics Subcommittee and to the entire TLV® Committee. For reasons that are unclear to the CMA-IAM Panel, the ACGIH did not allow the Panel an opportunity to present verbal comments and it is uncertain if copies of our written letters or other information were provided to either the subcommittee or committee members. The "sulfuric acid contained in strong inorganic acid mists" classification as a suspect human carcinogen was approved by these groups without significant review, along with approximately 200 other carcinogen classifications.

The CMA-IAM Panel subsequently challenged the ACGIH classification, pointing out the problems with the epidemiology studies that had been considered by IARC. The Panel also pointed out that animal studies on sulfuric acid mist were negative and that sulfuric acid mist did not meet the ACGIH definition for an "A2-suspected human carcinogen" classification. ACGIH did reply, indicating that "although available studies of workers exposed in the manufacture of sulfuric acid and exposed in processes using strong inorganic acid mists containing sulfuric acid provide conflicting or insufficient data to confirm an increased risk of cancer, ACGIH and the TLV Committee consider the data adequate to meet the Committee's definition of *Suspected Human Carcinogen*". A copy of that letter is attached as is a copy of their definition of an A2-Suspected Human Carcinogen.

The ACGIH definition includes two sentences. The first sentence states: "The agent is carcinogenic in experimental animals at dose levels, by route(s) of administration, at site(s), of histologic type(s), or by mechanism(s) that are considered relevant to worker exposure." The second sentence states that: "Available epidemiologic studies are conflicting or insufficient to confirm an increased risk of cancer in exposed humans." The CMA-IAM panel agrees with

ACGIH that the epidemiologic information is best characterized as insufficient. We disagree that epidemiologic evidence that is conflicting or insufficient is adequate to classify any substance as a suspect human carcinogen. We also believe that the ACGIH A2 definition was intended for use in situations where there are positive animal data considered to be relevant to human exposure and for which epidemiologic data (if any) are insufficient to justify the higher classification of known human carcinogen. ACGIH has not yet responded to our argument that sulfuric acid mist does not meet their A2 definition.

III. ANIMAL STUDIES

At the time IARC reviewed sulfuric acid and classified "occupational exposure to strong inorganic acid mist containing sulfuric acid" as a known human carcinogen, they did not review any lifetime animal studies. We have subsequently discovered that three lifetime animal studies were conducted in the 1970s under sponsorship of US government agencies. All three of these studies were negative. While negative studies do not prove that a substance is not a carcinogen, it is very unusual to find a chemical substance that has caused cancer in humans but is negative in multiple long term animal studies. This finding should cause the peer review groups to carefully look at the conflicts between, and problems within, the epidemiology studies. Given the fact that the animal studies are negative, the epidemiological evidence should be clearly convincing before sulfuric acid mist is classified as a known or suspected human carcinogen.

The Environmental Protection Agency (EPA) sponsored a large study conducted by the Institute of Environmental Medicine of the New York University Medical Center in the mid 1970s. This study involved 600 male Syrian hamsters. Hamsters were exposed to 100 mg/m^3 sulfuric acid mist for 6 hours/day, 5 days/ week for their lifetime. No respiratory tract tumors were seen in any of the animals. No excess of tumors was seen at other sites in either this study or the NIEHS sponsored studies. There was also no synergistic or promoting effect when this dose was administered in combination with benzo (a) pyrene, an animal carcinogen. A copy of this report is enclosed. This study has been reviewed by Swenberg and Beauchamp in a recently published peer reviewed article (copy attached).[2]

The National Institute for Environmental Health Sciences (NIEHS) sponsored two studies conducted by Becton, Dickson and Company. These were lifetime studies in Fischer 344 rats and in guinea pigs. The animals were exposed to 10 mg/m^3 of sulfuric acid mist for two years. A coincident study included exposure to 0.5 ppm of ozone along with exposure to 10 mg/m^3 of sulfuric acid mist. In neither study were any cancers of the respiratory tract noted.

We have not been able to locate copies of the complete study reports but are enclosing a copy of an abstract and copies of interim pathology reports.

We suspect these three animal studies were performed at about the time that catalytic converters were being installed on automobiles. When the results came back negative, the concern from sulfuric acid mist being generated by the converters was probably thought to have been addressed and the studies were not submitted for publication, but rather filed away by the government agencies.

IV. EPIDEMIOLOGY STUDIES

A number of epidemiology studies have been published that explored possible associations between sulfuric acid mist exposure and various cancers (particularly cancers of the larynx, lung, and nasopharynx). Most of these studies were not designed to look primarily at acid mist exposures. Exposure assessment was limited in all of the studies. These were the studies reviewed by IARC and Sathiakumar, et al. We will comment on key studies that were previously reviewed by these groups as well as on two additional studies that were not reviewed by these groups, namely a study by Suarez-Almazor, et al. and one by Coggon, et al.[3,4] Copies of these latter two studies are enclosed.

Since most epidemiology studies are retrospective in design, there are invariably problems associated with them. Some of the more serious problems include: inadequate control of confounding variables, selection bias, information bias, lack of quantitative exposure assessment, incomplete case ascertainment, small study size, and misclassification of cases and controls.

All of the available studies looking at a potential association between sulfuric acid mist exposure and cancer have multiple problems. In particular, there is no quantitative exposure assessment in any study and most studies have no measured exposures at all. Potentially confounding exposures to other known or suspected workplace carcinogens were not controlled in any of the studies. Most studies that attempted to control for known risk factors for cancer of the larynx (smoking and alcohol consumption) did not do so adequately. In fact, where there were attempts to control for alcohol consumption, it was often limited to whether the subject reported ever drinking alcoholic beverages or not. No study attempted to control for the known synergistic effects of combined heavy smoking and heavy alcohol consumption. Also, none of the studies considered the possible confounding by gastroesophageal reflux disease (GERD), a recently identified risk factor for laryngeal cancer.[5]

Given the inherent limitations in epidemiology studies, scientists look for a number of factors in deciding whether the data might support causal hypotheses. Some of the important factors include: consistency between studies, magnitude of

the apparent associations, positive dose-response relationships, biological plausibility, absence of bias, temporal relationship, control of confounding, and consistency with findings in animal and laboratory experiments. There are no studies among those reviewed by IARC that adequately address selection bias, information bias and control for confounding in the same study. While some key studies appear to demonstrate positive-dose response relationships and have apparently high odds ratios, if one looks at these key studies in more detail and includes results from newer studies, the evidence supporting a causal hypothesis is very weak.

Both the IARC review and the review by Sathiakumar, et al. identified cancer of the larynx and exposure to acid mist as the only association supporting a possible causal link between acid mist exposure and cancer. Our comments will therefore focus on studies related to cancer of the larynx and acid mist exposure. It appears that the key studies identified by IARC and Sathiakumar, et al. are the two case-control studies by Soskolne, et al.[6,7] and the cohort study by Steenland, et al.[8]

The first of the two Soskolne studies reported a very strong dose response relationship between categories of exposure and cancer of the larynx. Based on interviews with plant personnel, jobs were categorized as no/low sulfuric acid exposure, intermediate exposure, or high exposure. Odds ratios were calculated and reported in the paper as 1.0 for the no/low group, 4.6 (0.8-25) for the intermediate group, and 13.4 (2.1-86) for the high group. These results were based on an exposure index called mean grade. "Mean grade" was defined as the cumulative exposure divided by the total time exposed. When dose was specified as cumulative grade-years, there was also a reported positive association which was much smaller (1.0, 1.1, and 1.8 for no/low, intermediate, and high, respectively). These results appear to show a high magnitude of risk and a positive dose-response. However, these results are in marked contrast to those reported by Suarez-Almazor, et al.[3] Soskolne was the second author on this paper. In this paper when a "cumulative exposure index" (CEI) is used, the odds ratios are 1.0, 0.58, and 0.70 for the no/low, intermediate, and high exposure categories respectively. The CEI is the more traditional exposure metric used to explore relationships between exposures and chronic diseases such as cancer. In this reanalysis of Soskolne's earlier paper there is actually a negative dose-response between exposure to sulfuric acid mist and cancer of the larynx. If one looks at Table Two of this paper one notes that for the "mean grade" analysis there appears to be a deficit of cases in the no/low referent category rather than an excess in the intermediate and high categories. This is possibly an artifact that is responsible for the apparent strong dose-response relationship reported in the original paper. While Soskolne, et al. claim the choice of using "mean grade" was an *a priori* decision, we are not aware of any documentation to this effect. In any case, we believe the use of cumulative exposure is more appropriate.

In the second case-control study by Soskolne, et al., the authors used interview data previously collected for a Southern Ontario study on the effects of tobacco, alcohol, asbestos, and nickel on cancer of the larynx. Since this study had been performed to study other potential causes, there were no interview questions on exposure to sulfuric acid. In this study one of the authors ranked potential exposure based on job title, industry and era. Jobs were coded as to likelihood of exposure, degree of exposure, and frequency of exposure. There was no validation study of the rankings assigned by one individual who reportedly did the rankings blinded to the case or referent status. This study reported positive dose response relationships with several analytical approaches. This type of study is more rigorous from an epidemiologic perspective than the other Soskolne, et al. paper and the results appear internally consistent between the various methods of analysis.

Our concern with this paper lies with the method of exposure assessment and the lack of consistency with another similar study performed in Texas that was negative.[9] In the Soskolne, et al. Study, the overall ranking for possible sulfuric acid exposure was 72.7% for cases and 51.4% for referents. This compares to a 9% possible sulfuric acid exposure for the combined cases/referents quoted for a Montreal study by the authors. It is extremely unlikely that such a high proportion of either the referents or controls could have potential exposure to sulfuric acid even if they lived and worked in a community with a high level of manufacturing. From our experience, the percentage of workers within a sulfuric acid manufacturing plant with potential exposure to sulfuric acid would be much lower than that estimate for the referents. In our opinion, lack of credibility in the exposure assessment of this study undermines the results of the epidemiologic analysis. Further, since the study results are the opposite of what was seen in a similar study performed in Texas, we believe it should not be relied upon to assess the hypothesis that sulfuric acid mist exposure may be associated with cancer of the larynx.

Steenland, et al. reported a Standardized Incidence Ratio (SIR) of 2.6 for cancer of the larynx in their study of workers employed in metal pickling. Sathiakumar, et al. found this study to be of questionable validity for the following reasons: 23% of the original cohort was excluded for lack of medical information potentially causing a selection bias that could account for some of the excess; attempts to control for smoking and alcohol use demonstrated that these factors appeared to account for some of the excess; and there was no evidence that the Standardized Incidence Rate (SIR) varied with time since first exposure. It should be noted that the average exposure to sulfuric acid mist was estimated to have been 0.2 mg/m^3.

The results of the Steenland study are in marked contrast to the study of Coggon, et al. which was published in 1996. In the Coggon study there was no excess risk of mortality for cancers of the larynx, lung or nasopharynx. In fact, the Standardized Mortality Ratio (SMR) for cancer of the larynx was reported as 0.48

among those definitely exposed to sulfuric acid mist. Only one additional case of cancer of the larynx was identified through a search for living cases. Considering the relatively high cure rate for this cancer, one can conclude that an SIR for cancer of the larynx would be well below one (1.0) for this cohort. Exposures for this cohort were reported as either below 1.0 mg/m^3 or above 1.0 mg/m^3. A higher proportion of workers were in the higher exposure category. The overall level of exposure is much higher than that reported by Steenland. If the results of the Steenland study had really been due to exposure to acid mists, one would have expected an even higher rate of cancer of the larynx in the Coggon study. Such a result was not seen, in fact, the results were a negative SMR. Such inconsistencies should cast serious doubt on the causal hypothesis raised in the Steenland study.

The CMA-IAM Panel would like to point out that the authors of the Coggon study claim their results support previously reported positive results.[4] We disagree.[10] The results are positive only when they include cancers of the lip, tonsil, gum, and tongue with other respiratory tract cancers in the nested case-control analysis. The authors call this grouping "upper aerodigestive cancers" and claim it was formed *a priori*.[11] While the CMA-IAM Panel does not have any information to dispute that claim, the grouping called "upper aerodigestive cancers" certainly seems unconventional. The Panel does not believe it is appropriate to include those types of cancers, which are not part of the respiratory tract, in a combined analysis. While the term upper aerodigestive cancers has been used by others, it is usually used to combine cancers of the esophagus with cancers of the larynx where exposure to proteolytic enzymes from gastric juice is felt to have a possible etiologic role on these two types of cancer. For example, cigarette smoking and/or heavy alcohol consumption can lead to gastric reflux which in turn can expose the esophagus and larynx to severe irritation from proteolytic enzymes. This coupled with the other possible effects of cigarette smoking may explain the synergistic action of heavy alcohol consumption and cigarette smoking on these two types of cancer.

Interestingly, in a study in dogs it has been shown that both acid and pepsin are needed to cause irreversible injury when dogs have had a mucosal subglottic lesion created.[5] In this study, the lesions were painted with saline, acid, pepsin, or acid plus pepsin. The lesions in the acid only group healed whereas those in the acid plus pepsin group did not. It appeared that the pepsin was critical to the production of irreversible injury. The implication is that the pepsin in acidic gastric juice is the likely critical factor for an association between GERD and cancer of the larynx, and that this association is not related simply to the pH of gastric juice. One could speculate that this study suggests that possible pH changes from inhalation of acid mists would <u>not</u> be sufficient to cause an increased risk of cancer of the larynx.

In summary, The CMA-IAM Panel asserts that all of the key epidemiology studies relied upon by IARC are seriously flawed. These studies are either inconsistent with other studies using similar methodologies, or inconsistent with subsequent more appropriate reanalysis of the same data, or have exposure

assessment problems that render the studies unreliable. One might argue that the majority of studies reviewed by IARC were positive. While this may be correct, most of these studies have even more flaws than the key studies noted above (see Sathiakumar, et al.). In addition, there is a publication bias in favor of positive studies, because there is a tendency to not even submit negative studies for publication (as demonstrated by the negative animal studies conducted by EPA and NIEHS discussed above).

CONCLUSION

As stated in the introduction, the CMA-IAM Panel asserts that the scientific evidence available on sulfuric acid mist does not support classification as a known human carcinogen or as reasonably anticipated to be a human carcinogen. Sulfuric acid mist has been evaluated in three different animal species during lifetime exposures to high or very high levels of sulfuric acid mist. No respiratory tract tumors were seen in any of these studies due to sulfuric acid mist exposure. In addition, when combined with exposure to benzo (a) pyrene, no excess tumors were seen that were attributable to sulfuric acid mist. While several epidemiology studies have shown positive associations between sulfuric acid mist exposure and cancer of the larynx, all of these studies have serious flaws. At least two of the studies that purport to be positive are in fact negative when one looks only at respiratory tract tumors or when one reanalyzes the data using conventional indices of exposure. There are significant inconsistencies among studies with some that used similar methodologies showing opposite results. Also, one study with some of the higher exposures is negative while another study of the same basic industry (metal pickling) is positive even though the exposures reported were lower.[3,6] We believe these epidemiology studies when viewed in their entirety are conflicting and insufficient. Based on the weight of the evidence, these studies do not support listing sulfuric acid mist as a known or reasonably anticipated human carcinogen.

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ACGIH American Conference of Governmental Industrial Hygienists

July 12, 1996

Carol R. Stack, Ph.D.
Manager
Inorganic Acid Mists Panel
Chemical Manufacturers Association
1300 Wilson Boulevard
Arlington, VA 22209

Dear Dr. Stack:

On behalf of the American Conference of Governmental Industrial Hygienists (ACGIH), this letter is to inform you of the Conference's intent to clarify the recently adopted A2, *Suspected Human Carcinogen*, carcinogenicity designation for sulfuric acid. The A2 designation is to be identified with sulfuric acid contained in strong inorganic acid mists/liquid aerosols and is not intended for sulfuric acid per se. Although available studies of workers exposed in the manufacture of sulfuric acid and exposed in processes producing strong inorganic acid mists containing sulfuric acid provide conflicting or insufficient data to confirm an increased risk of cancer, ACGIH and the TLV Committee consider the data adequate to meet the Committee's definition of *Suspected Human Carcinogen* (enclosure).

Sulfuric acid will be included in the adopted list of substances to be published in the 1996 TLVs and BEIs Booklet. The A2 designation will carry a footnote stating: "Sulfuric acid contained in strong inorganic acid mists."

To further explore the issue of sulfuric acid and its potential as a carcinogen, a meeting has been scheduled for October 5, 1996, by the TLV Dusts and Inorganics Subcommittee with representatives of the Inorganic Acid Mists Panel of the Chemical Manufacturers Association. Substantive data that may evolve from such a meeting or from additional human or experimental animal exposure studies may enable the Committee to reconsider the appropriateness of the recommended TLV and the need for a Notice of Intended Change.

Thank you for your interest and contribution to the activities and deliberations of the TLV Committee.

Sincerely,

Roy M. Buchan
Chair

RMB:cs

Encl.

cc: ACGIH Board of Directors
TLV Chemical Substances Committee

ADOPTED APPENDICES

APPENDIX A: Carcinogenicity

The Chemical Substances TLV Committee has been aware of the increasing public concern over chemicals or industrial processes that cause or contribute to increased risk of cancer in workers. More sophisticated methods of bioassay, as well as the use of sophisticated mathematical models that extrapolate the levels of risk among workers, have led to differing interpretations as to which chemicals or processes should be categorized as human carcinogens and what the maximum exposure levels should be. The goal of the Committee has been to synthesize the available information in a manner that will be useful to practicing industrial hygienists, without overburdening them with needless details. The categories for carcinogenicity are:

A1 — *Confirmed Human Carcinogen:* The agent is carcinogenic to humans based on the weight of evidence from epidemiologic studies of, or convincing clinical evidence in, exposed humans.

A2 — *Suspected Human Carcinogen:* The agent is carcinogenic in experimental animals at dose levels, by route(s) of administration, at site(s), of histologic type(s), or by mechanism(s) that are considered relevant to worker exposure. Available epidemiologic studies are conflicting or insufficient to confirm an increased risk of cancer in exposed humans.

A3 — *Animal Carcinogen:* The agent is carcinogenic in experimental animals at a relatively high dose, by route(s) of administration, at site(s), of histologic type(s), or by mechanism(s) that are not considered relevant to worker exposure. Available epidemiologic studies do not confirm an increased risk of cancer in exposed humans. Available evidence suggests that the agent is not likely to cause cancer in humans except under uncommon or unlikely routes or levels of exposure.

A4 — *Not Classifiable as a Human Carcinogen:* There are inadequate data on which to classify the agent in terms of its carcinogenicity in humans and/or animals.

A5 — *Not Suspected as a Human Carcinogen:* The agent is not suspected to be a human carcinogen on the basis of properly conducted epidemiologic studies in humans. These studies have sufficiently long follow-up, reliable exposure histories, sufficiently high dose, and adequate statistical power to conclude that exposure to the agent does not convey a significant risk of cancer to humans. Evidence suggesting a lack of carcinogenicity in experimental animals will be considered if it is supported by other relevant data.

Substances for which no human or experimental animal carcinogenic data have been reported are assigned no carcinogenicity designation.

Exposures to carcinogens must be kept to a minimum. Workers exposed to A1 carcinogens without a TLV should be properly equipped to eliminate to the fullest extent possible all exposure to the carcinogen. For A1 carcinogens with a TLV and for A2 and A3 carcinogens, worker exposure by all routes should be carefully controlled to levels as low as possible below the TLV.